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RECENT DEVELOPMENTS IN THE EFFECTS OF SMOKING AND NICOTINE ON THE CARDIOVASCULAR SYSTEM OF MAN*

The controversy still exists as to whether smoking really has an effect on the cardiovascular system of man in health and in disease. During the past five years, various studies have been made on the effects of smoking and nicotine.

Earlier studies were carried out to determine whether the mechanical act of smoking, the cigarette paper, or the substances contained in the tobacco smoke produced constriction of the peripheral blood vessels during smoking. Many investigators presented evidence that the effects of smoking on the peripheral blood vessels were due to the absorbed portion of the tobacco smoke which contains pyridine bases, carbon monoxide and nicotine.

Recently, Kensler extended and reviewed the studies of the substances in smoke and indicated that smoke consists of two phases: (1) the liquid aerosol or particulate phase, containing a variety of aliphatic and aromatic alcohols, esters, sterols, aldehydes, ketones, acids, phenols, amino acids, vitamins, alkaloids such as nicotine, inorganic elements and free radicals; (2) a gas phase, containing carbon dioxide and monoxide, hydrogen cyanide and volatile hydrocarbons. However, it is most likely that these substances are not present in smoke in sufficient quantities to produce cardiovascular effects. Thus, nicotine is still the most important substance in smoke, and the constriction of the peripheral blood vessels produced by smoking cigarettes is analogous to that produced by a similar amount of nicotine.

Travell has shown that pH modified the absorption of nicotine from intact subcutaneous tissues and ligated stomach and urinary bladder in cats. At a pH of 5, it is absorbed slowly and animals survived doses of 20 to 50 mg./Kg. of nicotine, while at a pH of 6, absorption proceeds rapidly and 10 mg./Kg. may be fatal. An appreciable amount of nicotine can accumulate in the urinary bladder and cause acute toxicity if the urine is alkalinized.

The standard cigarette weighs 1 Gm. and contains 20 mg. of nicotine. According to Baumberger, when a cigarette is smoked, 35 per cent of the nicotine is destroyed at the burning tip, 35 per cent is lost in the side stream and much of this is given off to the environment; 22 per cent enters the mouth through the main stream of the smoke and the remaining 8 per cent remains in the unsmoked portion of the cigarette. It is estimated that 3 to 4 mg. of nicotine enter the respiratory passages, while from 2.5 to 3 mg. are absorbed by the lungs.

Larson, with newer techniques reported that during cigarette smoking only 10 per cent of the nicotine is absorbed by the noninhaler and 90 per cent by the person who inhales, while during cigar smoking slightly higher percentages are absorbed. If a tobacco quid is retained in the mouth for eight hours, tobacco chewers may absorb up to 90 per cent of the extraction from the quids, or as much as 88 mg. per day.

Mechanism of Action of Nicotine: Earlier workers attributed the vasoconstriction of the peripheral blood vessels, during smoking or the intravenous injection of nicotine, to the stimulation of the sympathetic nervous system, particularly the autonomic ganglia. Recent work by Pelikan suggested that nicotine may prevent

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ganglionic transmission by impairing the release of acetylcholine.

In 1948, Schmiterlöw showed in animals that norepinephrine was present in the wall of the peripheral arteries. Haimovici reported from perfusion experiments in animals that nicotine may act directly on the blood vessels because the vasoconstrictor action of nicotine occurs even after the removal of the sympathetic chains and the spinal nerves. A new concept was developed by Burn and Rand, who have shown in the rabbit that the constrictor action of nicotine may be due to a release of norepinephrine from the wall of the arteries, since the vasoconstrictor action of nicotine may not occur if there has been prior administration of reserpine which causes the norepinephrine to disappear.

Peripheral Circulation

That smoking causes constriction of the peripheral blood vessels, both in normal subjects and more conspicuously in those with peripheral vascular disease, is generally agreed. Roth et al. confirmed earlier work and pointed out that all methods of measuring blood flow in man are indirect and each has its own inherent error. Furthermore, irrespective of the method used, certain factors concerned with the status of the individual bear directly on the measurement of the blood flow in the extremities. These are the environmental temperature, the position of the subject, particularly of his extremities, the taking of food, and the basal metabolic rate. Any smoking test should consider these factors. When normal subjects smoke two-thirds of two cigarettes, no tolerance develops to tobacco with respect to the vascular effect. An elevation of blood pressure and pulse rate and a decrease of the skin temperature of the extremities occur. Nicotine appears to be the most important factor in producing the vascular effects. Although the oral administration of alcohol produces vasodilatation of the peripheral blood vessels, the vasoconstriction from smoking could not be prevented at any time during alcoholic vasodilatation.

In 1957, Nordenstam and Adams-Ray described the presence of chromaffin tissue in the human skin. Later, Burn and co-workers studied the effects of nicotine on the perfused vessels of rabbits' ears treated with reserpine and found that nicotine no longer produced vasoconstriction because of the depletion of norepinephrine and epinephrine. Therefore, they suggested that peripheral vascular disease could be explained by a hypersensitivity to the action of nicotine in releasing catecholamines from chromaffin tissue located near the blood vessels of the skin.

As a result of the work of Burn and Rand on animals, Stromblad injected nicotine into the brachial artery of healthy subjects. Subsequently, nicotine caused vasoconstriction in the hand. Sympathicolytics and ganglion-blocking agents abolished the effect of nicotine. This appears consistent with the assumption that nicotine causes a release of sympathicomimetics from the chromaffin system in the human skin, but could also be explained by the existence of a peripheral nervous plexus, containing ganglion cells.

Watts found that injections of nicotine in animals or smoking of tobacco by normal men produced an increased secretion of epinephrine, but not of norepinephrine, in the urine.

In contrast, Rehder and Roth found no appreciable rise in the levels of the fasting blood sugar and the epinephrine-like substances in the venous blood in normal subjects during smoking. However, the blood pressure and pulse rate were significantly raised and the skin temperatures of the fingers and toes were decreased.

Previously, it had been shown in the rabbit that the constrictor action of nicotine was unaffected by degeneration of all sympathetic fibers to the ear after removal of the stellate and superior cervical ganglia. Rapaport, Frank and Massell, and Roth and Shick found no vasoconstriction in the lower extremities in patients during smoking if bilateral lumbar sympathetic ganglionectomy of the first and second lumbar ganglia was complete, but a considerable fall in the skin temperatures of the fingers occurred. Thus, the remainder of the sympathetic nervous system seemed to function in a more than adequate manner.

Freund and Ward did not find significant changes following smoking in patients with peripheral vascular disease, but stated that variation in pathology in their patients and, in part, the decreased reactivity of tissue may account for the lack of significant change as compared to normals.

Eckstein and Horsley obtained venous pressure volume curves and venous pressures simultaneously from the forearm before and after the injection of 1 mg. of nicotine in 5 ml. of normal saline. This produced constriction sufficient to push blood from the forearm, but there was no change in venous pressure.

Eckstein et al. found that smoking reduced the blood flow in the foot in 90 per cent of their 31 tests carried out in a warm room, a cool room, and after 24 to 48 hours of abstinence from tobacco. The average decrease was similar. Apparently, these different control levels of vasomotor activity do not alter significantly the vasoconstrictive effects of smoking cigarettes. Smoking was a less intense vasoconstricting stimulus than cooling the environment from 83 F. to 68 F.

Rottenstein et al. determined the blood flow in skeletal muscle of normal men before and after intravenous injection of nicotine by the venous occlusion plethysmograph and Hensel thermoelectric needle, after skin blanching with adrenalin

iontophoresis. Cutaneous temperature of the toes was similarly obtained. After nicotine, the cutaneous flow decreased and by both methods of measurement the muscle blood flow increased; this increase subsided within six minutes while cutaneous vasoconstriction was prolonged.

Juergens compared the incidence and extent of smoking of 400 men with peripheral arteriosclerosis obliterans and an approximate number without peripheral vascular disease. At the onset of symptoms of peripheral arteriosclerosis, 97.5 per cent of the men were smokers, while only 2.5 per cent were nonsmokers. The incidence of smoking in men less than 60 years of age with arteriosclerosis was significantly higher than in those patients who had no evidence of the disease. Likewise, a nonsmoker rarely, if ever, is seen with thromboangiitis obliterans. Various reports have been made of the relief of symptoms of this disease after cessation of smoking.

In view of this, a word about filtered cigarettes is important, as there has been an implication that there is a definite added safety factor in filtered cigarettes. Previous studies have shown that the physiological effects of smoking cigarettes with a filter were not different from those of smoking ordinary or "denicotinized" cigarettes. The chemical laboratory of the American Medical Association has reported that the fraction of nicotine removed from the main stream of the smoke by the filter is small (approximately 5 per cent). Wright and others have reported a relapse in thromboangiitis obliterans, with reactivation of the disease, after smoking filtered cigarettes.

Much investigative work has been done to establish the fact that hypersensitivity to tobacco exists in cases of thromboangiitis obliterans and to a lesser extent in cases of coronary heart disease. Fontana et al. demonstrated that 33 per cent of the smokers with positive skin reactions to tobacco had some other allergic conditions when compared with 10 per cent of the smokers who did not react to skin tests. On smoking, 23 per cent of smokers with positive skin tests to tobacco had a fall in skin temperatures of the extremities, while only 4 per cent of the smokers with negative skin tests had changes in skin temperatures.

Harkavy reported that skin tests of 57 patients with coronary artery disease during 1958-59 showed that 59.6 per cent of those who smoked had positive skin tests, while 29.6 per cent had negative reactions along with 10.7 per cent of the nonsmokers. The average age of onset of acute coronary artery disease was as follows: 56 years for smokers with positive skin tests, 65 years for smokers nonsensitive to tobacco, and 69 years for nonsmokers with negative skin tests.

In contrast, in 1959 Armen and Cohen studied the effects of forced inhalation of tobacco smoke on rabbits previously sensitized to tobacco proteins. They concluded that the cardiovascular effects demonstrated by abnormalities of the electrocardiogram were due to anoxia and not to immunological effects.

Haag, in an extensive review, pointed out that there was need for further animal investigation to serve as a sound immunological basis for arriving at valid clinical concepts of possible tobacco-linked disease conditions.

Effects of Tobacco or Nicotine on the Heart

Most investigators agree that smoking, or the intravenous injection of nicotine, produces an increase in pulse rate and blood pressure and some flattening of the T waves of the electrocardiogram. Extensive studies have been carried out to determine whether these results were due to increased work of the heart or to coronary constriction.

As early as 1938, Graybiel, Starr and White reported that a few individuals were susceptible to small amounts of nicotine absorbed during smoking, but the occasional attacks of angina pectoris precipitated by smoking were not the result of coronary vasoconstriction but of a sudden increase in the work of the heart, as shown by the increase in blood pressure or pulse rate or both. In contrast, in 1941, Bellet and Kershbaum administered nicotine to dogs before and after ligation of a coronary artery. After ligation, only a fourth as much nicotine as before operation was required to produce the marked electrocardiographic changes. Later, in 1951, Burn and Grewal concluded that smoking may produce coronary constriction in man as a result of the release of posterior pituitary hormones.

Turning to the past five years, extensive experimental and clinical studies have been carried out to resolve this controversy. After intracoronary arterial injections of nicotine, West et al., working on dogs, concluded that there was no evidence of coronary constriction following the administration of nicotine. The results indicated that chemoreceptors, parasympathetic and sympathetic or sympathetic-like ganglia (chromaffin tissue) affected by nicotine are present in the heart and that the type of response depends on the predominant ganglia or receptors stimulated at the site of the injection. The electrocardiographic changes produced in their animals by intracoronary injections of nicotine,epinephrine and norepinephrine were similar to those described in man after intravenous administration of nicotine and during cigarette smoking. Their studies further suggested that anginal attacks associated with smoking are referable to increased cardiac work resulting from the sympathomimetic effects.

Forte et al. studied intact dogs during an infusion with nicotine and found that in these animals the oxygen supply was increased sufficiently to meet the greater myocardial oxygen demand

without any unfavorable effect on mechanical efficiency if the coronary arteries were normal.

Kien, Lasker and Sherrod determined the effect of cigarette smoke on the open-chest anesthetized dog. They suggested that the electrocardiographic disturbances subsequent to the inhalation of cigarette smoke were not due entirely to increased cardiac work or the coronary vasoconstriction, but rather to decreased oxygen utilization.

A new concept was introduced by Burn and Rand who demonstrated that the stimulant action of nicotine on the isolated atria of the hearts of rabbits was due to a release of noradrenalin and adrenalin from the stores within the heart. Such stores of these amines could be depleted by giving reserpine, and subsequently nicotine did not stimulate the depleted atria. The stores of noradrenalin and adrenalin in the normal heart exert some effect and accelerate the spontaneous rate of the heart. They concluded that smoking can liberate noradrenalin and adrenalin from the stores within the heart and thereby produce acceleration of the rate, and may cause or exaggerate ventricular arrhythmias.

Atherosclerosis: Travell and Rinzler showed that blood flow in the perfused coronary arteries of normal rabbits was increased after the injection of nicotine, while rabbits which had been made atherosclerotic by high cholesterol diets had a decline in flow through the perfused coronary vessels after nicotine. Likewise, nicotine caused transient sagging depression of the S-T segment of the electrocardiogram, characteristic of coronary insufficiency, in about 10 per cent of atherosclerotic rabbits but in none of the controls.

Wenzel et al. studied the effect of graded oral doses of nicotine plus a high cholesterol-fortified diet in rabbits. The nicotine-cholesterol group demonstrated greater mortality as well as greater electrocardiographic and pathological evidence of cardiac involvement and peripheral vascular changes than did the cholesterol or nicotine groups alone.

On the other hand, Page and Lewis observed that smoking of two nonfilter tip cigarettes by habitual smokers or nonsmokers was without effect in modifying cholesterol or lipoprotein concentrations during the 30-minute period immediately after smoking. Blackburn et al. compared cardiovascular and related characteristics of habitual smokers and nonsmokers in a group of men 17 to 67 years old in the United States and Finland. If the excess cardiovascular mortality in smokers was due to smoking, it was not mediated by obesity or elevated blood pressure and probably not by elevated serum cholesterol.

In 1957, Bargeron and co-workers carried out on man the first investigations using direct catheterization of the coronary sinus and a needle in the femoral artery. They found that smoking a cigarette caused a significant rise in coronary blood flow and heart rate, a significant decline in coronary vascular resistance and myocardial extraction of oxygen and glucose. Thus, smoking did not produce constriction of the coronary blood vessels in normal subjects.

Regan, Hellems and Bing compared the effects of smoking on normal individuals and patients with coronary heart disease (none in congestive failure). In normals, a significant rise in coronary blood flow and heart rate and a significant decline in coronary vascular resistance and myocardial extraction of oxygen were noted. In patients with coronary artery disease, coronary blood flow and myocardial oxygen extraction was unchanged except for a small decline in a few cases, but the pulse rate, systemic arterial pressure, cardiac output, and work increased. These changes increased the ratio work over oxygen consumption. Thus, the anginal pain experienced in some individuals during smoking may be the result of increased work of the heart rather than decreased coronary blood flow.

Electrocardiographic Findings: Before smoking or the injection of nicotine in men, von Ahn produced hypoxia of the myocardium and coronary insufficiency by the inspiration of oxygen-poor gases. He concluded that it is unlikely that the electrocardiographic changes provoked by smoking or injection of nicotine during hypoxia in persons with clinically healthy hearts were of coronary origin, but that they were probably secondary to increased heart rate.

Ballistocardiographic Findings: Starr first used the ballistocardiogram to record the stroke volume of the heart to determine the cardiac output.

Many refinements have been made in the ballistocardiograph and numerous studies have been carried out. Apparently the high incidence of abnormal ballistocardiograms among older persons limits the value of this method in persons more than 50 years of age. The relative frequency of normal records from those less than 50 years old who have clinical evidence of coronary disease likewise impairs the diagnostic usefulness of this instrument.

Davis and his group, after extensive studies, demonstrated that patients with ischemic heart disease reacted with ballistocardiographic deterioration much more frequently after smoking than did apparently normal subjects. They indicated that this "test" should be considered more of a challenge to the clinical investigators than a routine clinical procedure.

Strober studied the effects of smoking on 2,736 male subjects at an Air Force base. Most of the subjects had normal ballistocardiograms, but a rapidly increasing incidence of abnormal ballistocardiograms occurred with increasing age; 72.7 per cent of those in the 45 to 51 year group responded positively. Thus, this test may detect

asymptomatic coronary artery disease. Also, of the 120 smokers in the obese group, 45 per cent had abnormal tracings after smoking; whereas, in the nonobese group, 3.6 per cent had abnormal tracings. Brozek and Keys noted no significant differences in relative weight, arm diameter corrected for subcutaneous fat (as a measure of muscularity), or body density between a group of middle-aged business and professional men who never smoked and a group who were heavy smokers.

Master and others pointed out that at rest peripheral vascular disease may produce an abnormal ballistocardiogram in the absence of cardiac disease, but when cardiac disease is evident together with peripheral vascular disease, all the ballistocardiograms are abnormal.

Russek and co-workers likewise reported that in the case of the ballistocardiogram, the nicotine response is based primarily on peripheral vascular constriction and not on alterations in coronary blood flow.

Thomas and her associates have carried out a series of studies to determine the effect of smoking on healthy medical students by means of the ballistocardiograph. Changes in blood pressure, pulse, cardiac output and stroke volume were observed after smoking one cigarette. There was variability but the individual changes were consistent. Those with a family history of hypertension had an increased cardiac output and those with family histories of coronary disease generally showed a lowered cardiac output. When the same subjects were tested in a similar manner after several years, the results were the same. Comparison of the responses of blood pressure and heart rate to both the smoking test and the cold pressor test did not correlate well and independent information seemed to be gained from each test. Accordingly, both tests may contribute to the appraisal of individual circulatory reactivity, and one test did not replace the other.

Summary

Smoking or the injection of nicotine produces transient vascular effects on the heart and blood vessels and no tolerance develops to tobacco with respect to the vascular effects. Oral administration of alcohol does not prevent the constriction which develops during smoking.

Of the men with peripheral arteriosclerosis, 97.5 per cent were smokers and 2.5 per cent nonsmokers. The incidence is similar in patients with thromboangiitis obliterans.

While the ballistocardiograph is considered by some workers as not being ready for use in diagnosis, it has proved an interesting method for investigation. The findings of abnormal ballistocardiograms before and after smoking in the offspring of hypertensive parents and after smoking in the offspring of parents with coronary heart disease are of great interest.

Experimental evidence indicates that smoking or the injection of nicotine does not produce coronary constriction, as there is a significant rise in coronary blood flow but a definite decline in coronary vascular resistance and myocardial extraction of oxygen and glucose. Apparently, if the coronary blood vessels are normal the oxygen supply is increased sufficiently to meet the greater myocardial oxygen demand without any unfavorable effect on mechanical efficiency. However, if anginal pain occurs in some individuals during smoking, it may be the result of increased work of the heart due to sympathomimetic effects.

The most provocative experimental work is that of Burn and Rand who suggested that peripheral vascular disease could be explained by a sensitivity to the action of nicotine, which releases catecholamines from chromaffin tissue located near the blood vessels of the skin. Likewise, they demonstrated that the stimulant action of nicotine on the isolated atria of the hearts of rabbits was due to a release of adrenalin and noradrenalin from the stores of the heart. They concluded that smoking can liberate noradrenalin and adrenalin from the stores within the heart and thereby produce acceleration of the rate and may cause or exaggerate ventricular arrhythmias. These investigations were substantiated in part in humans by Stromblad, who injected nicotine into the brachial artery of normal subjects and found that the vasoconstriction produced by nicotine could be abolished with sympathicolytics and ganglion-blocking agents.

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SUPPLEMENTARY READING

1. Kensler, C. J.: Components of pharmacologic interest in tobacco smoke. Conference on Cardiovascular Effects of Nicotine and Smoking, New York Academy of Sciences, Sect. of Biol. and Med. Sc., New York, March 24-26, 1960.
2. Travell, J.: Influence of pH on absorption of nicotine from urinary bladder and subcutaneous tissues. Proc. Soc. Exper. Biol. & Med. 45: 552, 1940.
3. Baumberger, J. P.: Nicotine content of tobacco smoke. J. Pharmacol. & Exper. Therap. 21: 35, 1923.
4. Larson, P. S.: Absorption of nicotine under various conditions of tobacco use. Conference on Cardiovascular Effects of Nicotine and Smoking, New York Academy of Sciences, Sect. of Biol. and Med. Sc., New York, March 24-26, 1960.
5. Pelikan, E. W., and Garcia, G. C.: Ganglionic "blockade" by nicotine, morphine, tea and hexamethonium (abstr.). Fed. Proc. 18: 432, 1959.
6. Schmiterlöw, C. G.: Nature and occurrence of pressor and depressor substances in extracts from blood vessels. Acta physiol. scandinav. Suppl. 56, 1948.
7. Haimovici, H.: Postganglionic site of action of nicotine with special reference to its direct action on blood vessels. Proc. Soc. Exper. Biol. & Med. 68: 516, 1948.
8. Burn, J. H., and Rand, M. J.: Effects of catechol amines present in peripheral tissues. J. Physiol. 140: 7 (Proceedings), 1958.
9. Roth, G. M.: Tobacco and the Cardiovascular System: Effects of Smoking and of Nicotine on Normal Persons. Springfield, Ill., Charles C Thomas, 1951.

10. Nordenstam, H., and Adams-Ray, J.: Chromaffin granules and their cellular location in human skin. Zschr. Zellforsch. **45**: 435, 1957.

11. Burn, J. H., and Rand, M. J.: Noradrenaline in artery walls and its dispersal by reserpine. Brit. Med. J. (No. 5076) **1**: 903, 1958.

12. Stromblad, B. C.: Effect of intra-arterially administered nicotine on the blood flow in the hand. Brit. Med. J. (No. 5120) **1**: 484, 1959.

13. Watts, D. T., and Bragg, A. D.: Effect of smoking on the urinary output of epinephrine and norepinephrine in man. J. Appl. Physiol. **9**: 275, 1956.

14. Rehder, K., and Roth, G. M.: Effect of smoking on the fasting blood sugar and pressor amines. Circulation **20**: 224, 1959.

15. Rapaport, S. I., Frank, H. A., and Massell, T. B.: Effect of smoking upon the blood flow in the sympathectomized limb. Circulation **2**: 850, 1950.

16. Roth, G. M., and Shick, R. M.: Effects of smoking on the peripheral circulation. Dis. Chest **37**: 203, 1960.

17. Freund, J., and Ward, C.: Acute effects of cigarette smoking on the digital circulation in patients with peripheral vascular disease (abstr.). Proceedings of the 32nd Scientific Sessions, American Heart Association, October, 1959, p. 696.

18. Eckstein, J. W., and Horsley, A. W.: Responses of the peripheral veins in man to the intravenous administration of nicotine. Conference on Cardiovascular Effects of Nicotine and Smoking, New York Academy of Sciences, Sect. of Biol. and Med. Sc., New York, March 24-26, 1960.

19. Eckstein, J. W., Wood, J. E., and Wilkins, R. W.: Comparative vasoconstrictor effects of inhaling tobacco smoke in warm and cool environments and before and after abstinence from tobacco. Am. Heart J. **53**: 455, 1957.

20. Rottenstein, H., Peirce, G., Ellier, R., Felder, D. J., and Montgomery, H.: Effect of nicotine on muscle blood flow in man. Proceedings of the 32nd Scientific Sessions, American Heart Association, October, 1959, p. 760.

21. Juergens, J. L., Barker, N. W., and Hines, E. A., Jr.: Arteriosclerosis obliterans: Review of 520 cases with special reference to pathogenic and prognosis factors. Circulation **21**: 188, 1960.

22. Chemical Laboratory: Study of cigarettes, cigarette smoke and filters. J.A.M.A. **157**: 1309, 1955.

23. Wright, I. S.: Cigarettes. J.A.M.A. **155**: 666, 1954.

24. Fontana, V. J., Redisch, W., Nemir, R. L., Smith, M. K., DeCrinis, K., and Sulzberger, M. B.: Studies in tobacco hypersensitivity: III. Reactions to skin tests and peripheral vascular responses. J. Allergy **30**: 241, 1959.

25. Harkavy, J.: Tobacco allergy in vascular diseases. Rev. Allergy & Appl. Immunology **11**: 189, 1957.

26. Armen, R. N., and Cohen, S.: Effect of forced inhalation of tobacco smoke on the electrocardiogram of normal and tobacco-sensitized rabbits. Dis. Chest **35**: 663, 1959.

27. Silvette, H., Larson, P. S., and Haag, H. B.: Immunological aspects of tobacco and smoking. Am. J. Med. Sc. **234**: 561, 1957.

28. Graybiel, A., Starr, R. S., and White, P. D.: Electrocardiographic changes following the inhalation of tobacco smoke. Am. Heart J. **15**: 89, 1938.

29. Bellet, S., Kershbaum, A., Meade, R. H., Jr., and Schwartz, L.: Effects of tobacco smoke and nicotine on the normal heart and in the presence of myocardial damage produced by coronary ligation. Am. J. Med. Sc. **201**: 40, 1941.

30. Burn, G. P., and Grewal, R. S.: Antidiuretic response to and excretion of pituitary (posterior lobe) extract in man, with reference to the action of nicotine. Brit. J. Pharmacol. **6**: 471, 1951.

31. West, J. W., Guzman, S. V., and Bellet, S.: Cardiac effects of intracoronary arterial injections of nicotine. Circulation Research **6**: 389, 1958.

32. Forte, I. E., Williams, A. J., Potgieter, L., Schmitthenner, J. E., Hafkenschiel, J. H., and Riegel, C.: Coronary blood flow and cardiac oxygen metabolism during nicotine-induced increases in left ventricular pressure work. Conference on Cardiovascular Effects of Nicotine and Smoking, New York Academy of Sciences, Sect. of Biol. and Med. Sc., New York, March 24-26, 1960.

33. Kien, G. A., Lasker, N., and Sherrod, T. R.: Action of cigarette smoke on cardiovascular hemodynamics and oxygen utilization in the dog. J. Pharmacol. & Exper. Therap. **124**: 35, 1958.

34. Travell, J., Karp, D., and Rinzler, S. H.: Nicotine effects on normal and atherosclerotic rabbit hearts (abstr.). Fed. Proc. **16**: 341, 1957. Full-length paper in press. Travell, J., Rinzler, S. H., and Karp, D.: Cardiac effects of nicotine in the rabbit with experimental coronary atherosclerosis. *In* Cardiovascular Effects of Nicotine and Smoking (monograph), New York Academy of Sciences.

35. Wenzel, D. G., Turner, J. A., and Kissil, D.: Effect of nicotine on cholesterol-induced atherosclerosis in the rabbit. Circulation Research **7**: 256, 1959.

36. Page, I. H., Lewis, L. A., and Moinuddin, M.: Effect of cigarette smoking on serum cholesterol and lipoprotein concentrations. J.A.M.A. **171**: 1500, 1959.

37. Blackburn, H., Brozek, J., Taylor, H. L., and Keys, A.: Comparison of cardiovascular and related characteristics in habitual smokers and non-smokers. Conference on Cardiovascular Effects of Nicotine and Smoking, New York Academy of Sciences, Sect. of Biol. and Med. Sc., New York, March 24-26, 1960.

38. Bargeron, L. M., Jr., Ehmke, D., Gonlubol, F., Castellanos, A., Siegel, A., and Bing, R. J.: Effect of cigarette smoking on coronary blood flow and myocardial metabolism. Circulation **15**: 251, 1957.

39. Regan, T. J., Hellems, H. K., and Bing, R. J.: Effect of cigarette smoking on coronary circulation in normal individuals and in patients with coronary heart disease. Conference on Cardiovascular Effects of Nicotine and Smoking, New York Academy of Sciences, Sect. of Biol. and Med. Sc., New York, March 24-26, 1960.

40. von Ahn, B.: Acute effect of tobacco-smoking and nicotine on the electrocardiogram especially during induced hypoxia: Clinical and experimental investigation. Acta med. scandinav. Suppl. 292, 1954.

41. Starr, I., and Hildreth, E. A.: Changes in the ballistocardiograms of healthy persons and of patients, in most cases followed for a period of 10 years or longer. Tr. A. Am. Physicians **64**: 59, 1951.

42. Scarborough, W. R., and Talbot, S. A.: Proposals for ballistocardiographic nomenclature and conventions: Revised and extended report of Committee on Ballistocardiographic Terminology. Circulation **14**: 435, 1956.

43. Davis, F. W., Jr., Scarborough, W. R., Mason, R. E., Singewald, M. L., and Baker, B. M., Jr.: Ballistocardiographic cigarette test: Further observations. Am. Heart J. **51**: 165, 1956.

44. Strober, M.: Effect of the Dock cigarette smoking test on the ballistocardiogram: Survey of a normal male population. Proj. Reports U. S. Air Force School of Aviation Medicine (Randolph Field, Texas), Report No. 56-56, May, 1956.

45. Brozek, J., and Keys, A.: Smoking and body composition. Fed. Proc. **16**: 16, 1957.

46. Master, A. M., Donoso, E., Pordy, L., and Chesky, K.: Ballistocardiogram in peripheral vascular disease. Am. Heart J. **46**: 180, 1953.

47. Russek, H. I., Zohman, B. L., and Dorset, V. J.: Effects of tobacco and whiskey on the cardiovascular system. J.A.M.A. **157**: 563, 1955.

48. Thomas, C. B., Bateman, J. L., Lindberg, E. F., and Bornhold, H. J.: Observations on the individual effects of smoking on the blood pressure, heart rate, stroke volume and cardiac output of healthy young adults. Ann. Int. Med. **44**: 874, 1956.

49. Thomas, C. B., and Murphy, E. A.: Circulatory response to smoking: Variation in ballistocardiographic smoking tests in healthy young men. J. Chronic Dis. **8**: 202, 1958.

50. Thomas, C. B., and Murphy, E. A.: Observations on some possible precursors of essential hypertension and coronary artery disease: VI. Comparison of the circulatory reactivity to the cold pressor test and to the smoking test. Ann. Int. Med. **50**: 970, 1959.

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